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Microarray methods to identify factors determining breast cancer progression: Potentials, limitations, and challenges

B. van der Vegt [a], G.H. de Bock [b], H. Hollema [a], J. Wesseling [c,*]

[a] *Department of Pathology and Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[b] *Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[c] *Department of Pathology, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands*

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* Corresponding author. Tel.: +31 20 5122750; fax: +31 20 5122759.
E-mail address: j.wesseling@nki.nl (J. Wesseling).

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Abstract

65–80% of the patients with breast cancer might not benefit from the adjuvant therapy they receive based on 'classical' markers used for the selection for adjuvant therapy. Therefore it is necessary to develop new markers that are able to tailor treatment for an individual patient. A number of microarray methods have been developed in recent years to accommodate this search for new factors that determine breast cancer progression. We give an overview of the most commonly used microarray methods to identify tumour progression markers (oligo- or cDNA arrays, CGH arrays, PCR arrays, and tissue microarrays). Their applications will be illustrated using the most influential examples from literature. The potentials, limitations and the related statistical analyses of each method are discussed. We conclude that microarray studies have led to an increase in the understanding of the complexity and diversity of breast carcinoma and have provided clinical relevant subgroups of breast cancer that may benefit from patient tailored treatment. Still, more extensive external validation and long-term follow-up will be necessary before such assays can be implemented into routine clinical practice. Most likely, these novel prognostic indicators will be complementary to the already available classical prognostic factors.

Keywords: Breast carcinoma; Tissue microarray; RT-PCR; DNA-microarray; Prognosis; Classification

1. Introduction

In the Western world, the life time risk for developing breast cancer in women is approximately 10%. 5–7% of patients present with distant metastases at the time of diagnosis, but 30–40% will develop metastases and die of the disease within 15 years [1]. Currently, selection for adjuvant chemotherapy is based on generally accepted prognostic and predictive factors including age, tumour size, histological grade, hormone receptor status, Her2/neu status, menopausal status and lymph node status [2,3]. Although these factors perform relatively well in group-based statistics, they poorly predict the outcome for the individual patient. This because prediction of prognosis and response to (neo-)adjuvant treatment in breast cancer is far from optimal as it is a very heterogeneous disease comprising many biological subtypes. In addition, it is hard to predict which of the undetected micrometastatic deposits, which are present in approximately 30% of patients with stages I, II, or III breast cancer, make it to macrometastatic lesions [4]. In the period 1998–2002 adjuvant chemotherapy was given to ca. 90% of breast cancer patients younger than 35 years, to 55% of breast cancer patients 35–50 years of age, and to 20% of breast cancer patients 50–70 years of age ($n = 8437$; Netherlands Cancer Registry; http://www.ikcnet.nl/page.php?id=97) to treat micrometastases that go undetected at the time of diagnosis. If chemotherapy is given, the relative risk of reduction of relapse within 10 years is reduced with approximately 35% among women aged under 50 and approximately 20% among those aged 50–70 [5], as confirmed by the 15 year follow-up analysis [1]. However these studies also show that substantial numbers of patients considered high-risk who did not receive adjuvant therapy in the old trials did not develop distant metastases, implying that many patients currently treated with adjuvant therapy are actually overtreated. This underlines the importance of good prediction strategies to tailor treatment for each individual patient [6]. In recent years many microarray procedures have been developed which made it possible, from genome to protein, to assess multiple factors (e.g. the expression of many genes or proteins) per patient in one experiment and relate them to clinical endpoints. With these techniques it has become possible to differentiate between clinically relevant breast cancer subtypes and to search for new prognostic indicators in breast cancer.

In this review we give an overview of the currently used microarray methods and their applications will be illustrated using the most influential examples from literature. The potentials and limitations and the related statistical analyses of each method will be discussed.

2. DNA microarrays

2.1. Technique

2.1.1. General principle

The DNA microarray technique was first described by Fodor et al. [7]. Using this technique up to 50,000 known single stranded DNA fragments are immobilized at predefined spots on a solid surface [8]. Using the natural quality of DNA to bind complementary DNA, study samples can be tested for gene expression. In this way, thousands of genomic or gene expression features of one tumour sample can be assessed in a single test.